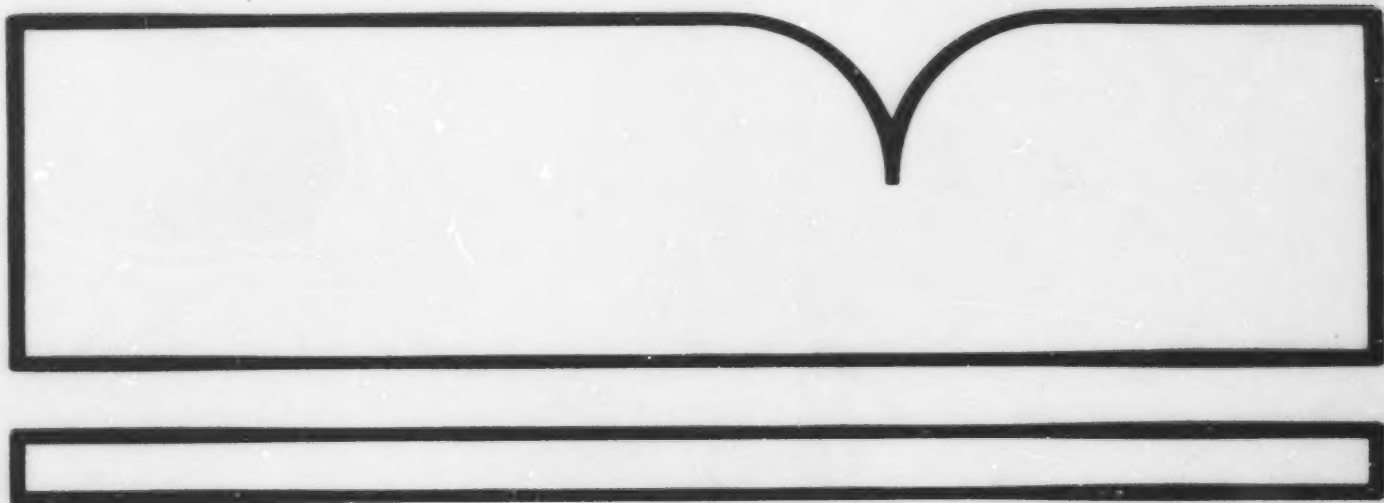


Drinking Water Criteria Document for
2(2,4,5-Trichlorophenoxy)Propionic Acid
(2,4,5-TP) (Final Draft)

(U.S.) Environmental Protection Agency
Cincinnati, OH

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Research and Development

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DRINKING WATER CRITERIA DOCUMENT FOR 2(2,4,5-TRICHLOROPHENOXY)PROPIONIC ACID (2,4,5-TP)

Prepared for

OFFICE OF DRINKING WATER

Prepared by

Environmental Criteria and
Assessment Office
Cincinnati OH 45268

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
a.e.	Acid equivalent
bw	Body weight
CNS	Central nervous system
DNA	Deoxyribonucleic acid
ED ₅₀	Median effective dose
HA	Health Advisory
i.v.	Intravenous
LD ₅₀	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse effect level
LOEL	Lowest-observed-effect level
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
RNA	Ribonucleic acid
s.c.	Subcutaneous
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
2,4,5-T	2,4,5-Trichlorophenoxy acetic acid
2,4,5-TP	2,4,5-Trichlorophenoxypropionic acid
TWA	Time weighted average
UV	Ultraviolet

I. SUMMARY

2,4,5-Trichlorophenoxypropionic acid (2,4,5-TP) is a commonly used systemic herbicide for both agricultural and nonagricultural purposes. The commercial herbicide is contaminated to varying extent with 2,3,7,8-TCDD, a highly toxic tetra-chlorinated dibenzo-p-dioxin. The use of such contaminated products in toxicity testing may affect both the qualitative and quantitative interpretation of results as related per se to 2,4,5-TP. The toxicokinetic profile of 2,4,5-TP indicates that this compound is rapidly and extensively absorbed by mammals following oral exposure and, by analogy to 2,4,5-L, would be anticipated to have a high degree of binding to plasma protein and tissue. Excretion of unchanged 2,4,5-TP suggests that 2,4,5-TP is not metabolized extensively by rats. The urine is the predominant route of excretion and is rapid.

Acute oral exposure to 2,4,5-TP causes a variety of physiological (muscular weakness, depression) and biochemical (>SGPT and SGOT) effects on mammals. The liver and kidney appear to be the target organs following prolonged exposure to this compound.

2,4,5-TP has been found to cause teratogenic effects on both mice and rats. Although contamination of 2,4,5-TP by 2,3,7,8-TCDD may contribute to the teratogenic and reproductive effects of this compound, the extent of this interaction is unclear.

2,4,5-TP has been investigated for carcinogenic activity. At this time, 2,4,5-TP is not considered oncogenic. 2,4,5-TP has produced negative results in mutagenicity assays with bacteria.

The quantification of toxicological effects of 2,4,5-TP involved the identification of levels at which adverse health effects are anticipated for both chronic and acute exposures for adults and children consuming 2 or 1 $\frac{1}{2}$ water/day, respectively. A level of 0.75 mg/ $\frac{1}{2}$ (1.4 mg/day) was derived for an adult exposed to 2,4,5-TP in water for 10 days. This level declined to 0.26 mg/ $\frac{1}{2}$ (0.53 mg/day) for lifetime exposure in an adult. For a child, a level of 0.20 mg/ $\frac{1}{2}$ (0.20 mg/day) was derived for a 10-day exposure period.

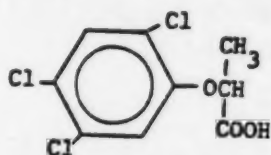
Pertinent data regarding the effects on animals or humans as a result of acute exposure to 2,4,5-TP could not be located in the available literature; therefore, no 1-day HA could be derived.

II. GENERAL INFORMATION AND PROPERTIES

Structures, Molecular Weights and Synonyms

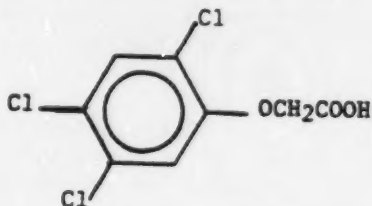
Since 2,4,5-T will be discussed for comparison purposes in some of the sections to follow, its physical and chemical properties will be presented here along with those of 2,4,5-TP.

2(2,4,5-trichlorophenoxy)propionic acid (2,4,5-TP), Silvex, Fenoprop



Molecular weight: 269.5

2,4,5-Trichlorophenoxy acetic acid (2,4,5-T)



Molecular weight: 255.5

Chemical Abstract Service (CAS) Number and Registry of Toxic Effects of Chemical Substances (RTECS) Number

2,4,5-TP CAS Number: 93-72-1

RTECS Number: UF8225000

2,4,5-T CAS Number: 93-765

RTECS Number: AJ8400000

Chemical/Physical Characteristics (taken from Weed Science Society of America, 1979, unless otherwise stated)

2(2,4,5-Trichlorophenoxy)-propionic acid (2,4,5-TP) is a white powder used to control woody plants, broadleaf herbaceous weeds and aquatic weeds. It is also used as a selective postemergence herbicide in rice farming and, in sugarcane production, it controls weeds not susceptible to 2,4-dichlorophenoxyacetic acid (2,4-D).

- Melting point: 178.2°C
- Specific gravity: Powder density (at 30°C) 1.640 bulk density, 27.4 lb/cu. ft.
- Solubility in water: 140 ppm at 25°C
- pK_a: 2.83 (Cessna and Grover, 1978)
- Carbon tetrachloride: 860 ppm at 26°C
Ester formulations are highly soluble in petroleum derivative solvents and are only slightly soluble in water (usual carrier: oil and oil-water mixture).
- Spectroscopic data: UV absorption maximum 209, 287, 295 (NRCC, 1978) IR absorption bands in cm⁻¹ 815, 863 (NRCC, 1978)
- Commercial synthesis: Reaction of 2,4,5-trichlorophenol with methyl ester of alpha-chloropropionic acid in the presence of methanol and sodium methoxide and acidification of the product (Esposito et al., 1980). Reactivity: should react with organic and inorganic bases to form salts and with alcohols to form esters.

The herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), when pure, is a white crystalline solid. As a systemic herbicide, it is used for both agricultural and nonagricultural purposes. The three commonly used application techniques for this herbicide are aerial application, ground application and injection on basal application (Norris, 1980).

Melting Point: 154-155°C
 More than 400 formulated pesticide products in the market contain the salts of ester forms of 2,4,5-T as active ingredients (Esposito et al., 1980). The commercial products of 2,4,5-T are used as cropland weed control (i.e., in rice fields) and in noncropland weed control (i.e., for aquatic and broadleaf weeds) in the control of woody plants and rights of ways, and in the management of forests, pastures, fallow and rangelands (Ramanujam, 1981).

Decomposition temperature: Probably >200°C; stable at its melting point

Specific Gravity: 1.662 at 30°C

Vapor Pressure: 6.46×10^{-6} (25°C) (Khan, 1985)

Solubility:
 Water: 237 ppm at 30°C; 189 ppm at 20°C (NRCC, 1978).
 Ethanol: 548 g/l (NRCC, 1978)
 Amine salts are soluble in water and slightly soluble in petroleum oils; esters are slightly soluble in water and soluble in petroleum oils (usual carrier: water, oil or oil-water emulsion).

Spectroscopic data: Ultraviolet absorption maxima in nm: 207, 289 and 297
 Infrared absorption bands cm^{-1} : 764, 680

Commercial Synthesis: Reaction of 2,4,5-trichlorophenol with monochloroacetic acid under alkaline conditions.

Reactivity: Reacts with organic and inorganic bases to form salts and with alcohols to form esters (IARC, 1977).

No analyses of 2,4,5-TP were found in the available literature; however, the impurities in 2,4,5-TP will probably not be similar in nature to those in 2,4,5-T, since 2,4,5-trichlorophenol is the starting material for both

products. The following list is an analysis for technical 2,4,5-T (Bovey, 1980). Whenever acetic acid derivatives are present, propionic acid derivatives would be expected in 2,4,5-TP. Impurities may vary among producers and among batches of the same producer (Bovey, 1980).

91.0 ± 1.0	2,4,5-T
0.5 ± 0.1	2,4,5-trichloroanisole
2.0 ± 0.5	5-methoxy(2,4-dichlorophenoxy)acetic acid
2.0 ± 0.5	2-methoxy-4,5-dichlorophenoxyacetic acid
0.3 ± 0.1	2,4,5-trichlorophenol
3.0 ± 0.5	bis-2,4,5-trichlorophenoxyacetic acid
0.3 ± 0.1	2,5-dichlorophenoxyacetic acid
0.2 ± 0.1	SO ₄
0.2 ± 0.1	Sodium salt of 2,4,5-T
0.5 ± 0.2	H ₂ O
<0.1 ppm	2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) required for registration of the product with the U.S. EPA.

Conversion factors for relating concentrations in air of some 2,4,5-TP esters are listed in Table II-1.

Summary

2(2,4,5-Trichlorophenoxy)propionic acid (mol. wt. 269.5), commonly known as 2,4,5-TP, is a white powder used as an herbicide. The pure compound has a melting point of 178.2°C, a specific gravity of 1.640 at 30°C, a water solubility of 140 ppm at 25°C and a carbon tetrachloride solubility of 860 ppm at 26°C. Esters of 2,4,5-TP are slightly water soluble but highly soluble in petroleum solvents.

TABLE II-1
Conversion Factors for Some 2,4,5-TP Esters

Ester	Conversion Factors
methyl	1 ppm = 11.6 mg/m ³ 1 mg/m ³ = 0.0859 ppm
ethyl	1 ppm = 12.2 mg/m ³ 1 mg/m ³ = 0.0819 ppm
propyl (1- or 2-)	1 ppm = 12.8 mg/m ³ 1 mg/m ³ = 0.0782 ppm
butyl	1 ppm = 13.4 mg/m ³ 1 mg/m ³ = 0.0749 ppm
butoxy ethyl	1 ppm = 15.2 mg/m ³ 1 mg/m ³ = 0.0660 ppm
propylene glycol butyl ether	1 ppm = 16.4 mg/m ³ 1 mg/m ³ = 0.0610 ppm

III. TOXICOKINETICS

Limited data describing the toxicokinetic profile of 2,4,5-TP were located in the available literature. Structural and metabolic considerations indicate that 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and 2,4,5-TP will probably behave similarly; therefore, some data on the toxicokinetics of 2,4,5-T are provided.

Animal Studies

Review articles have been published on the fate of phenoxy acids in mammals (Gehring and Betso, 1978; Leng, 1977).

Absorption. Ingestion of 2,4,5-TP and 2,4,5-T by mammals was followed by rapid and efficient absorption (up to 98-100% after small doses) from the gastrointestinal tract (Erne, 1966; NRCC, 1978). More than 90% of single oral doses of 2,4,5-T (0.17-41 mg/kg, given by Fang et al., 1973 or 100-200 mg/kg by Piper et al., 1973) were assimilated from the digestive tract of rats. Reabsorption of biliary-excreted 2,4,5-T was virtually complete (Eaton, 1982), which may contribute to a longer half-life and greater bioavailability.

The 2,4,5-T derived esters may be absorbed less readily than the acids and salts, by comparison with previous work with 2,4-D (2,4-dichlorophenoxyacetic acid) (Erne, 1966; NRCC, 1978). Rats given single doses of 100 mg/kg bw of the amine salt of 2,4-D by gavage had peak plasma levels (>100 µg/ml) in 7 hours, while a similar dose of the butyl ester resulted in maximum plasma levels of <50 µg/ml. In studies with 2,4-D, only the

acid was detectable in the plasma or urine of rats, pigs and calves after an oral dose of the ester was administered, thus indicating that the ester undergoes hydrolysis. No data are available on the dermal or pulmonary absorption of 2,4,5-TP or 2,4,5-T in animals.

Distribution. Once the phenoxy acids are absorbed, they are rapidly distributed throughout the body. They are bound to plasma proteins, resulting in the retention in the plasma or extracellular compartments or both. Fang and Lindstrom (1980) reported that 2,4,5-T had the highest binding affinity to bovine serum albumin, in vitro, of several phenoxyacetic acids tested. There were two binding sites on the bovine serum albumin for 2,4,5-T and 2,4-D, while the other compounds had only one site. Senczuk and Pogorzelska (1981) reported in an abstract that 2,4,5-TP and 2,4,5-T blood levels remained high for 24-72 hours in rats treated with 50 mg of the compound.

Sauerhoff et al. (1976b) reported in an abstract that a single i.v. dose of 5 or 50 mg/kg of ^{14}C -2,4,5-TP to rats resulted in greater concentrations of ^{14}C activity in the liver and kidney than in the fat, brain or muscle at 18 and 216 hours postadministration. Sauerhoff et al. (1976a) indicated that the kidney tissue:blood concentration ratio was dose dependent in the range of 5-100 mg/kg bw of 2,4,5-T administered intravenously to rats.

Small amounts of these herbicides were transferred to the young through the mother's milk after the dams received two doses of 0.17 mg/kg after giving birth (exact times not mentioned) (Fang et al., 1973). Pregnant mice were given i.v. injections of radiolabeled 2,4,5-T at various times during pregnancy and whole body autoradiography was performed at various times after injection (Lindquist and Ullberg, 1971). The visceral yolk sac epithelium of pregnant mice accumulates 2,4,5-T to a greater concentration than that found in blood; 2,4,5-T is gradually transferred to the fetus at late stages of pregnancy but without accumulation (Lindquist and Ullberg, 1971). Selective uptake of 2,4,5-T into the yolk sac epithelium and the absence of placental transfer in early pregnancy are effects similar to those seen with trypan blue in mouse embryos (Lloyd and Beck, 1969).

Metabolism and Excretion. Following gavage administration of a single 100 or 200 mg/kg bw dose of 2,4,5-T and subsequent absorption, 2,4,5-T is eliminated unchanged from the body predominantly (>93% in rats) through the urine (Piper et al., 1973). Only small amounts of 2,4,5-T are conjugated before excretion. Urinary excretion of low doses of 2,4,5-T (0.17 mg/kg bw) is normally rapid in adult animals (3.2-hour average half-life for elimination from blood in rats), but appears to be extremely prolonged in neonates following exposure to an unquantified dose from the mother's milk (66-hour half-life for elimination from blood in rat pups) (Fang et al., 1973). This is perhaps due to the fact that in rats renal function is not complete for several weeks post partum. The fate of 2,4,5-T following a single oral administration of 5 mg/kg to rats and dogs revealed half-life values for 2,4,5-T clearance from plasma of 2.7 and 77.0 hours, respectively (Piper et

al., 1973). The prolonged retention of 2,4,5-T in dogs provides a reasonable explanation for the generally observed greater toxicity of 2,4,5-T in dogs than in rats.

The possibility of cumulative or progressive inhibition of renal organic anion transport was studied in vivo and in vitro in rats given a 2- or 3-week dietary regimen of 2,4,5-TP (doses up to 800 mg/kg diet) (Stroo et al., 1979). After dosing, renal excretion was evaluated in kidney slices or in vivo by the elimination of p-aminohippurate (PAH). Although 2,4,5-TP competitively inhibited PAH secretion, the rapid recovery within 24 hours of the last dose of normal secretion indicates that chronic anion transport blockage did not occur. In a study on the renal handling of 2,4,5-T in dogs, Hook et al. (1976) demonstrated that the low clearance of 2,4,5-T was due to the fact that 2,4,5-T was more tightly bound to plasma protein (i.e., decreased amount of free 2,4,5-T was available for excretion).

Pertinent data regarding metabolism and excretion in humans could not be located in the available literature.

Summary of Toxicokinetics

Absorption of 2,4,5-TP and 2,4,5-T by the gastrointestinal tract of mammals following oral exposure is rapid and virtually complete, with >90% absorbed after doses of 0.04-200 mg/kg (Fang et al., 1973; Piper et al., 1973; Erne, 1966). Data on absorption after dermal or inhalation exposure to 2,4,5-TP and 2,4,5-T were not available. Following absorption, these compounds are rapidly distributed throughout the organism, although reversible binding to plasma protein results in a greater retention in the plasma compartment (Fang and Lindstrom, 1980; Senczuk and Pogorzelska, 1981).

Highest tissue levels are associated with livers and kidneys (Erne, 1966; Sauerhoff et al., 1976b).

2,4,5-TP and 2,4,5-T are not metabolized extensively since >93% of the administered oral doses were excreted unchanged in the urine of rats (Sauerhoff et al., 1976a; Piper et al., 1973). Excretion of 2,4,5-T by rats was rapid ($t_{1/2}$ = 3.4 hours for adults; $t_{1/2}$ = 97 hours for neonates) (Fang et al., 1973). Urinary excretion of 2,4,5-TP and 2,4,5-T after high i.v. doses (50 and ≥ 100 mg/kg, respectively) to rats followed saturation kinetics, while a greater fraction was eliminated in feces, suggesting a greater role of biliary excretion at higher doses (Sauerhoff et al., 1976a,b).

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as 2,4,5-TP from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to 2,4,5-TP is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Detailed information concerning the occurrence of and exposure to 2,4,5-TP in the environment is presented in another document entitled "Occurrence of Pesticides in Drinking Water, Food and Air" (Johnston et al., 1984). This chapter summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

In the Exposure Estimation section of this chapter, available information is presented on the range of human exposure and intake for 2,4,5-TP from drinking water, food and ambient air for the 70-kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources.

Exposure Estimation

Drinking Water. Levels of 2,4,5-TP in drinking water vary from one location to another. The highest level of 2,4,5-TP monitored in the available studies was $>10 \mu\text{g/l}$ (the current Maximum Contaminant Level) in North Carolina (FRDS, 1984). However, levels of 2,4,5-TP in drinking water typically appear to be somewhat lower. Analysis of the National Screening Program for Organics in Drinking Water (NSP) (Boland, 1981) suggests that median levels of 2,4,5-TP in drinking water systems would be $<2.0 \mu\text{g/l}$, since none of 117 systems sampled contained a level of 2,4,5-TP $>2.0 \mu\text{g/l}$. In addition, median levels of 2,4,5-TP are likely to be $<0.1 \mu\text{g/l}$, since none of the 92 systems sampled in the Rural Water Survey (RWS) contained a level of 2,4,5-TP $>0.1 \mu\text{g/l}$ (U.S. EPA, 1984). 2,4,5-TP may not be present in drinking water in some areas. The available monitoring data are not sufficient to determine regional variations in exposure levels for 2,4,5-TP.

The daily intake of 2,4,5-TP from drinking water was estimated using the assumptions presented in Table IV-1 and the values presented above. The estimates in Table IV-1 indicate that the daily intake of 2,4,5-TP from drinking water ranges from 0.0- $>0.29 \mu\text{g/kg/day}$. However, the values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Diet. FDA reported that no significant dietary exposure to 2,4,5-TP is expected, based on the data in the FDA Total Diet Studies. Tolerances

TABLE IV-1

Estimated Intake of 2,4,5-TP from Drinking Water*

Drinking water concentration ($\mu\text{g}/\text{l}$)	Intake ($\mu\text{g}/\text{kg}/\text{day}$)
0.0	0.0
0.1	0.0029
2.0	0.057
>10	>0.29

*Assumptions: 70-kg man consuming 2 l of water/day.

set by U.S. EPA for 2,4,5-TP in and on raw agricultural commodities are 50 $\mu\text{g/kg}$ for pears and 100 $\mu\text{g/kg}$ in apples, plums, rice and sugarcane (FDA, 1981).

Air. No data were obtained on levels of 2,4,5-TP in ambient air. Therefore, the respiratory intake of 2,4,5-TP could not be estimated.

Summary

Data on the intake of 2,4,5-TP from drinking water, food and ambient air were insufficient for use in determining which of the three sources is the major contributor to total intake. U.S. EPA has reported a maximum safe level for 2,4,5-TP (from all sources) of 2 $\mu\text{g/kg/day}$ (U.S. EPA, 1976).

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V. HEALTH EFFECTS ON ANIMALS

One of the major problems in assessing the effects of 2,4,5-TP is the contamination with varying amounts of 2,3,7,8-TCDD. Many investigators were unaware of the presence and amount of 2,3,7,8-TCDD in a sample and, therefore, this information has gone unreported in many studies. Consequently, whether the reported effects are attributable to 2,4,5-TP alone, the 2,3,7,8-TCDD contaminant, a combination of both, or additional contaminants such as the carrier or emulsifier is not clear in many studies.

The subsequent discussion will concern itself with the toxic effects of 2,4,5-TP and only consider 2,3,7,8-TCDD in its relationship to the phenoxy herbicides 2,4,5-TP and 2,4,5-T. Appropriate notations for 2,3,7,8-TCDD content have been included in the tables on acute, subchronic and chronic toxicity, and "Contaminants" sections present limited quantitative data on the health effects of 2,3,7,8-TCDD.

Acute Effects

The single dose oral LD_{50} s for 2,4,5-TP range from ~600-1400 mg/kg bw for mice, rats, guinea pigs and rabbits for acid and ester formulations; for the acid, an LD_{50} of 650 mg/kg was determined in rats (Table V-1) (Rowe and Hymas, 1954). Gross general symptoms of intoxication include depression, posterior quarter muscle weakness, irritation of the stomach and minor liver and kidney damage. The mono-, di- and tripropylene glycol butyl ether esters are the least toxic formulations.

TABLE V-1

Acute Oral Toxicity of 2,4,5-TP (Acid, Ester, and Amine Formulations) in Experimental Animals^a

Species/Strain	Formulation/Vehicle	Purity/TCDD Content	Sex/No.	Dose (mg/kg bw) (19/20 confidence limits)	Effects
Mice/NR	PGBE esters ^b (mono-, di-, tri-)/corn oil	NR/NR	F/NR	1410 (1000-2000)	LD50
Rats/NR	acid/corn oil	NR/NR	M-F/NR	650 (560-760)	LD50
Rats/NR	mixed butyl esters/corn oil	NR/NR	F/NR	600 (250-1000)	LD50
Rats/NR	PGBE esters (mono-, di-, tri-)/corn oil	NR/NR	F/NR	621 (473-814)	LD50
Guinea pigs/NR	PGBE esters (mono-, di-, tri-)/corn oil	NR/NR	M/NR	1250 (range: 500-2000)	LD50
Rabbits/NR	mixed butyl esters/undiluted	NR/NR	F/NR	750 (500-1000)	LD50
Rabbits/NR	PGBE esters (mono-, di-, tri-)/undiluted	NR/NR	F/NR	819 (610-1070)	LD50

^aSource: Rowe and Hymas, 1954^bPGBE = propylene glycol butyl ether

NR = Not reported

Subchronic Exposure

Data on the subchronic toxicity of 2,4,5-TP in experimental animals are scarce. There are, however, data from two unpublished Dow Chemical Company reports available in a review document on phenoxy herbicides (NRCC, 1978). The data from these studies are summarized in Table V-2. Oral administration of 5 mg/kg bw/day of 2,4,5-TP to rats for 90 days in the diet produced histopathologic changes in the liver and kidney (Dow Chemical Company, 1962), whereas a dose of 2 mg/kg bw/day was reported to be a NOEL in dogs (parameters measured were not reported in NRCC, 1978) (Dow Chemical Company, 1963).

Chronic Exposure

The only information available on the chronic toxicity of 2,4,5-TP (other than an oncogenic study) comes from unpublished investigations in rats and dogs conducted by Dow Chemical Company. A 2-year dietary regimen of a potassium salt of 2,4,5-TP (0, 0.26, 0.8, 2.6 or 7.9 mg a.e./kg bw/day) only revealed a significant increase in relative kidney:body weight ratios in rats of both sexes at doses >0.26 mg a.e./kg bw/day (Gehring and Betso, 1978). Other parameters measured in this study were body weight, survival, food intake, clinical chemistry, hematology, tumor incidence and gross or histopathology. No effects were seen in these parameters except for a decrease in body weight at the highest dose. Because of the absence of morphological alterations in the kidney at any dose level, these investigators felt that the increase in kidney weight reflected a physiological adaptation rather than an adverse effect (Gehring and Betso, 1978).

TABLE V-2

Subchronic Oral Toxicity of 2,4,5-TP Formulations in Experimental Animals*

Species/ Strain	Formulation/ Vehicle	Purity/TCDD Content	Sex/No.	Age/wt.	Dose (mg/kg bw/day)	Duration	Effects
Rats/NR	sodium salt or PGRE ester/diet	NR/NR	M-F/NR	NR/NR	5 mg a.e.	90 days	Increase in relative weight of liver and kidney with "histopathologic changes" in both
Dogs/NR	NR/diet	NR/NR	NR/NR	NR/NR	2 mg a.e.	89 days	"no-effect level"

*Source: Dow Chemical Co., 1962, 1963

PGRE = propylene glycol butyl ether; a.e. = acid equivalent; NR = Not reported

TABLE V-3
Chronic Oral Toxicity of 2,4,5-TP Formulations in Experimental Animals

Species/Strain	Formulation/Vehicle	Purity/TCDD	Sex/No.	Age/wt.	Dose/Duration	Effect
Rats/Wistar	potassium salt/diet	NR/NR	M-F/30-30	NR/NR	0.26, 0.8, 2.6 or 7.9 mg a.e./kg bw/day x 2 years (some animals were sacrificed at 12 and 18 months)	no effect on survival, food intake, clinical chemistry, hematology, tumor incidence, gross pathology or histopathology; there was noted an increase in relative kidney weight at all doses in males and a decreased in body weight in males at the highest dose (statistical significances not specified)
Dogs/Beagle	potassium salt/diet	NR/NR	M-F/4-4	NR/NR	0.9 mg a.e./kg bw/day x 2 years	no effect on body weight, food intake, hematology, blood urea nitrogen, alkaline phosphatase, bromsulphthalein dye retention, organ weights, or histopathology
					2.6 mg a.e./kg bw/day x 2 years	mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation in males
					8.2, 9.9 mg a.e./kg bw/day x 2 years (in M and F, respectively)	same liver changes as described for intermediate dose in both males and females plus elevated levels of SGPT and SGOT in females

*Source: Gehring and Betso, 1978
a.e. = acid equivalents; NR = Not reported

Evidence of adverse effects on the livers of male dogs, however, was observed at 2.6 mg a.e./kg bw/day 2,4,5-TP. Both male and female dogs were affected at doses of 8.2 and 9.9 mg a.e./kg bw/day, respectively (Gehring and Betso, 1978). This 2-year feeding study of 2,4,5-TP resulted in mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation in females, accompanied by elevations of SGOT and SGPT levels (elevations were not specified by the author). A 0.9 mg kg a.e./kg bw/day was judged to be a NOAEL for the male dog and 2.6 mg/kg/day for female dogs.

Synergistic and Antagonistic Effects

The nature of the interaction between 2,4,5-TP and 2,3,7,8-TCDD is not well understood. In many studies, it is not clear whether the reported effects are due to 2,4,5-TP alone, the 2,3,7,8-TCDD contaminant or a combination of both. Further data regarding the interaction between 2,4,5-TP and 2,3,7,8-TCDD could not be located in the available literature.

Carcinogenicity

Innes et al. (1969) reported that tumor incidences were not increased at any site in B6C3F1 or B6AKF1 mice (18/sex/strain) that were treated daily by gavage from 7-28 days of age with 46.4 mg/kg bw/day of 2,4,5-TP, and subsequently maintained for 76-77 weeks on a diet that contained 121 ppm 2,4,5-TP. If it is assumed that mice consume 13% of their weight in feed each day, the estimated daily TWA dose of 2,4,5-TP was 17.2 mg/kg/day. Elevated incidences of tumors were also not observed at specific sites in the same strains of mice (18/sex/strain) 18 months after single s.c. injections of 215 mg/kg 2,4,5-TP (in DMSO) on day 28 of age. Complete necropsies that included gross and histological examination of major organs and tissues

were performed on all treated and control animals. Male B6C3F1 mice that were treated orally or by s.c. injection did show a higher incidence of total tumors (8/17 and 7/18 in treated vs. 22/79 and 2/24 in controls, respectively), but this was not apparent in female B6C3F1 or B6AKF1 mice of either sex.

Gehring and Betso (1978) reported that the Dow Chemical Company (unpublished studies) found no increased incidence of tumors in male or female Wistar rats that were fed 2,4,5-TP potassium salt at levels of 0, 0.26, 0.8, 2.6 or 7.9 mg a.e./kg bw/day for 2 years (see Table V-3). At each dose level 30 animals of each sex were initially treated, and 3-5 rats/sex/dose were selected for interim sacrifices at 12 and 18 months.

Present data indicate that 2,3,7,8-TCDD, a known contaminant of 2,4,5-TP, is carcinogenic in rats maintained on 2,3,7,8-TCDD supplemented diets for 2 years (Kociba et al., 1978). Rats fed 0.01 µg/kg bw/day 2,3,7,8-TCDD demonstrated an increased incidence of liver lesions (including hepatocellular nodules) and lung lesions (including focal alveolar hyperplasia). Ingestion of 0.1 µg/kg bw/day caused an increased incidence of hepatocellular carcinomas and squamous cell carcinomas of the lung, hard palate/nasal turbinates or tongue, compared with controls.

Mutagenicity

The mutagenicity of 2,4,5-TP was evaluated in a single study. In an Ames assay of over 100 herbicides for possible mutagenicity, Anderson et al. (1972) found that 2,4,5-TP failed to revert eight Salmonella typhimurium strains to histidine independence. The strains were not specified, but were

designated as nonsense (amber or ochre), missense or frameshift mutants (the mutations involved the C, D and G gene of the histidine operon). The plate incorporation technique was used, but a metabolic activation system was not employed. Approximately 1-5 μ l of the surveyed chemicals were applied per plate, but the specific concentration of 2,4,5-TP tested was not stated.

Teratogenicity and Other Reproductive Effects

Only two studies have been encountered on the potential teratogenic activity of 2,4,5-TP. Courtney (1977) administered 2,4,5-TP to pregnant CD-1 mice at a dose level of 1.5 mM/kg/day (~398 mg/kg/day) on days 12 through 15 of gestation. The compound was administered both by gavage using corn oil:acetone (9:1) as the vehicle and by s.c. injection using DMSO as the vehicle. Both administrations caused a significant ($p < 0.01$) increase in maternal weight, probably caused by increased liver weight, and a significant ($p < 0.01$) increase in maternal liver-to-body weight ratios. Both routes of exposure were also associated with a significant ($p < 0.01$) decrease in fetal weight. Oral and s.c. exposures to 2,4,5-TP were associated with slight incidences of cleft palate in total fetuses of 7 and 3%, respectively, and prenatal development indices of 88 and 66, respectively.

The other study on the teratogenicity of 2,4,5-TP is an unpublished study by Dow Chemical Company, summarized in U.S. EPA (1979a). Because the summary is so brief it is reproduced in full below:

Dow Chemical Company studied the reproductive effects of silvex and the propylene glycol butyl ether ester of silvex (silvex-PGBE), each containing < 0.05 ppm TCDD. Sprague-Dawley rats were exposed to 25-100 mg/kg of silvex on days 6-15 of gestation. Significant effects on fetal mortality and birth weight were observed in the litters of treated dams. Skeletal anomalies, such as cleft palate, retarded ossification and extra cervical ribs were observed among

the exposed fetuses. Microphthalmia (abnormal smallness of the eyeball) and cardiovascular abnormalities were also seen. Similar effects were observed when animals were dosed with silvex-PGBE, or when dosed for three-day intervals during the period of early organogenesis.

Contaminants

Early studies using 2,4,5-TP must be cautiously interpreted because the herbicide samples may have been contaminated with a high concentration of 2,3,7,8-TCDD. Reported effect/no-effect levels would be expected to be conservative, however, a higher content of 2,3,7,8-TCDD would most likely have suggested greater toxicity than would be the case if purer herbicide samples had been used. The 2,3,7,8-TCDD contaminant is highly toxic, with symptoms appearing at chronic doses as low as 0.01 $\mu\text{g/kg bw/day}$ in rats (Kociba et al., 1978). NOELs were reported at 0.001 mg/kg/day (22 ppt in the diet). The single oral LD_{50} for 2,3,7,8-TCDD ranges from 0.6 $\mu\text{g/kg}$ in male guinea pigs to 115 $\mu\text{g/kg}$ in rabbits (Schwetz et al., 1973). Mortality from acute oral poisoning is usually delayed, preceded by symptoms such as dehydration, alopecia and inactivity.

Summary

The acute oral LD_{50} for 2,4,5-TP for rats is 650 mg/kg (Rowe and Hymas, 1954). Subchronic exposure of 2,4,5-TP in rats (5 mg/kg/day for 90 days) produced histopathologic changes in the liver and kidney (Dow Chemical Company, 1962), whereas 2 mg/kg/day for 89 days was reported to be a NOEL in dogs (Dow Chemical Company, 1963). Adverse effects such as mild degeneration and necrosis of hepatocytes accompanied by elevations of SGOT and SGPT were observed in dogs fed 2.6, 8.2 and 9.9 mg/kg/day for 2 years (Gehring

and Betso, 1978). A 2-year dietary regimen of 2,4,5-TP revealed an increase in relative kidney:bw ratio in rats at doses >2.6 mg/kg/day (Gehring and Betso, 1978).

The nature of the interaction between 2,4,5-TP and 2,3,7,8-TCDD is not understood and pertinent data regarding this interaction could not be located in the available literature.

Limited data concerning the potential carcinogenicity of 2,4,5-TP are available. Chronic oral exposure to 2,4,5-TP did not elicit significantly increased incidences of tumors at any site in two strains of mice exposed to ~17.2 mg/kg/day for 80-81 weeks (Bionetics Research Laboratories, 1968; Innes, 1969), in rats exposed to 7.9 mg a.e./kg/day for 2 years (Gehring and Betso, 1978) or in dogs exposed to 9.9 mg a.e./kg/day for 2 years (Gehring and Betso, 1978).

Only two studies have been located on the potential teratogenic activity of 2,4,5-TP (Courtney, 1977; U.S. EPA, 1979a). Both studies reported teratogenic effects at dose levels of ~398 mg/kg/day and 25-100 mg/kg/day in mice and rats, respectively; however, the lack of conclusive evidence from these studies precludes the evaluation of the teratogenic potential of 2,4,5-TP. However, doses of 25-100 mg Silves-PGBE/kg bw containing <0.05 ppm TCDD did cause definite teratogenic effects in rats (U.S. EPA, 1979a).

VI. HEALTH EFFECTS ON HUMANS

Introduction

Observations in Humans. A primary risk to human health could arise from occupational exposure during the manufacture and use of 2,4,5-T and 2,4,5-TP. The available occupational studies, however, have assessed the effects of mixed exposures of chlorophenoxy herbicides (including 2,4,5-T), chlorophenols and other compounds. The design and results of occupational exposure studies that did not identify birth malformations or carcinogenic responses are summarized in Tables VI-1 and VI-2.

Acute Exposure

Pertinent data regarding the effects resulting from acute exposure of 2,4,5-TP to humans could not be located in the available literature.

Subchronic and Chronic Exposure

In a recent study of a cohort of 204 employees also engaged in the manufacture of 2,4,5-T and exposed from 1 month to 10 years, no adverse effects on mortality rates were uncovered (Ott et al., 1980). Maximum allowable 2,3,7,8-TCDD concentration in 2,4,5-T was <1 mg/kg in 1966 and <0.1 mg/kg in 1972. No episodes of chloracne or porphyria cutanea tarda were reported but there were complaints of nasal irritation caused by dust. Only one death (less than the number expected) was attributable to a malignant neoplasm. Workers were exposed to a number of other chemicals in the environment including styrenebutadiene latex (see Table VI-1).

In a study of 56 workers who were employed in the manufacture of 2,4,5-T and 2,4-D, Singer et al. (1982) reported a significant correlation ($p < 0.004$)

TABLE VI-1
Occupational Exposure Study that did not Identify Birth Malformations or Carcinogenic Responses*

Exposure	Study Population	Sex/No.	Control Group	Level of Exposure	Observation Period	Effects
2,4,5-T, 2,4,5-TP, 2,4,5-trichlorophenols 2,4-D, styrene-butadiene latex, 2-methyl-4-chlorophenoxyacetic acid	employees engaged in the manufacture of 2,4,5-T, exposed from 1 month to 10 years (reactor, salt wheel, acid wheel and dryer)	M/204	U.S. Vital Statistics (white, male population); previous experience of this plant	In 1969: concentrations of 2,4,5-T or its sodium salt ranged from <0.1-6.2 mg/m ³ for 60 samples (TWA airborne exposure estimated from 0.2-0.8 mg/m ³)	1950-1971	In 1970--levels of TCDD were <1 mg/kg using a wipe test dust levels were often irritating (nasal irritation, sneezing, bitter taste at levels of 0.1 mg/m ³); 19 episodes of acute exposure to 2,4,5-T or its esters (eye or skin contact); no adverse mortality effects (11 deaths compares favorably with U.S. white males); no episodes of chloracne or porphyria cutanea; only death due to malignant neoplasma (lower than expected).

*Source: Ott et al., 1980

TABLE VI-2
Epidemiological and Occupational Studies (Carcinogenicity)

Exposure	Study Population	Sex/No.	Control Group	Level of Exposure	Observation Period	Effects	Reference
Phenoxy herbicides aminotriazole, monuron	Swedish railroad workers exposed for more than 45 days	M/730	official statistics of Sweden for age and sex specific death rates and incidence rates	unknown	1957-1972	No excess for any of the 3 categories of cause of death (all causes, all tumors, or lung tumors) and no increased risk in tumor incidence was recorded for the cohort; phenoxy acids and combina- tions.	Axelsson and Sundell, 1974
Phenoxy herbicides aminotriazole	Swedish railroad workers exposed for more than 45 days	M/348	same as above	unknown	1957-1978	decrease in total mortality; increase in total tumors for workers exposed to both groups of compounds; a sig- nificant increase in stomach tumors in workers exposed to phenoxy herbicides alone when 10-year latency period was considered ($p<0.05$).	Axelsson et al., 1979
Phenoxy herbicides chlorophenols	Swedish railroad workers exposed for more than 45 days	M/348	same as above	unknown	1957-1961	In a subcohort of the above mentioned study in which exposure occurred before 1962, there was a signifi- cant ($p<0.05$) excess of total mortality, deaths due to all tumors ($p<0.025$) and deaths due to stomach cancer.	Axelsson et al., 1979
Phenoxy herbicides	northern Swedish patients with malignant mesen- chymal tumors	M/87	same as above	unknown	1970-1976	7/87 patients with malignant mesenchymal tumors had a history of exposure to phenoxy herbicides 10-20 years earlier; authors felt that no causal relationship between exposure and the development of these tumors could be made (4/7 were for- estry workers, 1/7 a sawmill worker, 1/7 a farm worker)	Hardell, 1977

TABLE VI-2 (cont.)

Exposure	Study Population	Sex/No.	Control Group	Level of Exposure	Observation Period	Effects	Reference
Phenoxy herbicides chlorophenols,	northern Swedish patients (living and deceased) with malignant mesen- chymal tumors admitted to University Hospital, Umea, Sweden	M/52 (31 were deceased)	4 matched controls* for each case (deceased cases matched with deceased controls); matched for sex, age (year of death), and place of residence, total of 208 controls (deaths from malig- nant tumors were excluded).	unknown	1970-1977	a questionnaire was sent to patients, next of kin, employers and controls; exposure to compounds in question was identified in 36.5% of the patients and 9.2% of controls; relative risk (RR) of developing soft-tissue sarcomas after exposure to phenoxy acetic acids only was calculated to be 5.3 ($p<0.001$); these phenoxy herbicides were known to contain dioxins and other impurities	Hardell and Sandstrom, 1979
Phenoxy herbicides chlorophenols	patients (living and deceased) with soft tissue sar- comas reported to Cancer Registry between 1974-78 (residents of 5 southern coun- ties of Sweden)	M/110 (38 were deceased)	2 matched controls* for each case (de- ceased cases matched with de- ceased controls); matched for resi- dence and age (and year of death); total of 219 con- trols (deaths from malignant tumors were excluded)	unknown	1969-1978	exposure (determined by questionnaire--see above) to the compounds in question was identified in 22.7% of the patients and 5.9% of controls; relative risk (RR) of develop- ing soft tissue sarcomas after exposure to phenoxy acids alone was 6.8 ($p<0.005$). (only 7 cases in this group) after exposure to phenoxy acids free of dioxins and dibenzofurans was 4.2 ($p<0.025$); RR of 6.4 obtained for exposed individuals in agriculture and forestry, compared to other occupations without exposure.	Eriksson et al., 1981
Phenoxy herbicides chlorophenols, organic solvents	patients (living) and deceased with malignant lymphoma, including Hodgkin disease (60) and non-Hodgkin lymphoma (109) admitted to University Hospital, Umea, Sweden	M/169	2 matched controls* for each case (deceased controls) matched for sex, age and residence (year of death); total of 338 con- trols (deaths from malignant tumors were excluded).	unknown	1974-1978	exposure was determined by questionnaire; exposure to phenoxy herbicides and chlorophenols was identified in 36.1% of the cases and 9.6% of the controls. RR of developing malignant lymphoma after exposure to phenoxy acids alone was 4.8 ($p<0.005$).	Hardell et al., 1981

*Taken from the National Population Registry

between duration of employment and reduction of nerve conduction velocities of sural nerves. Conduction velocities of the sural nerves of the phenoxy herbicide-exposed workers (average exposure = 7 years) was 40.3 m/second, while values for a control group of 25 nonexposed workers was 42.8 m/second ($p=0.02$). Singer et al. (1982) noted that these electrophysiologic responses may be due to the 2,4-D or 2,3,7,8-TCDD contaminants, and not to 2,4,5-T alone.

Information from six Scandinavian epidemiologic studies has been summarized in Table VI-2. These studies examine the association between occupational exposure to phenoxyacetic acid herbicides and the occurrences of cancer in man (Axelson and Sundell, 1974; Axelson et al., 1979; Hardell, 1977; Hardell and Sandstrom, 1979; Eriksson et al., 1981; Hardell et al., 1981). These studies collectively indicate an excess risk to the development of soft-tissue sarcomas and malignant lymphomas among men occupationally exposed to phenoxy herbicides.

The four most recent Swedish epidemiologic case control studies associate the development of soft-tissue sarcomas with exposure to phenoxy herbicides and require an extended discussion (Hardell and Sandstrom, 1979; Eriksson et al., 1981; Hardell, 1981; Hardell et al., 1981). Exposure information was obtained from questionnaires sent to living patients and employers or to relatives of deceased patients; this was supplemented by telephone conversations. This information was based largely on recall of events of many years before; recall bias could be a confounding aspect in ascertaining exposures. According to the authors, emphasis on phenoxy herbicide or chlorophenol exposure was avoided. These investigations all

utilized the same case-control methodology. The cases, all male and some deceased, had either soft-tissue sarcomas or malignant lymphomas (see Table VI-2). Living controls (2 or 4) were taken from the National Population Registry of Sweden and were matched for sex, age and place of residence. Deceased cases were matched with deceased controls by age, residence and year of death. Deaths from malignant tumors were excluded from the control population. The study conducted by Eriksson et al. (1981) in the southern counties of Sweden was initiated to see if the results of Hardell et al. (1981) could be duplicated in another region of Sweden. Subjects with exposure to phenoxy herbicides totalling <1 day were considered unexposed and, because of the latency period involved in the development of these malignancies, exposures occurring within 5 years before the year of diagnosis for the case were excluded.

The most recent publication on this subject is by Hardell (1981), in which an attempt is made to substantiate the validity of the technique used to assess exposure to phenoxy herbicides in the previous studies. The original data is reanalyzed and another cancer type (colon cancer) is used as an index series and as a reference for the rare tumors discussed in the earlier case series. No observational bias was found which could distort the previous findings and no significant association was found linking phenoxy herbicide exposure and colon cancer. A reanalysis of these data by the Carcinogen Assessment Group (CAG) of the U.S. EPA indicates that the associations reported in the Swedish soft tissue sarcoma studies are great enough that they are unlikely to have resulted entirely from random variation bias or confounding factors, even though this possibility cannot be dismissed (U.S. EPA, 1980).

Detailed knowledge on the formulation or dispersion agents of the phenoxy herbicides was not available. Although these studies included persons exposed to chlorophenols and organic solvents as well as the phenoxy herbicides, the statistical analyses (relative risk derived from odds ratio of exposed and nonexposed persons who had or had not developed disease) were performed separately on groups of individuals exposed to only one of these classifications of chemicals. The relative risk for exposure to phenoxy-acetic acids was 5.3 (Hardell and Sandstrom, 1979) and 6.8 (Eriksson et al., 1981). No attempt was made in any of the epidemiologic studies to quantify exposure.

In the investigations of Hardell et al. (1981) no attempt was made to separate exposures to 2,4,5-T and 2,4,5-TP (contaminated with dioxins and dibenzofurans) from any other phenoxy herbicide, such as 2,4-D or 2-chloro-2-methylphenoxyacetic acid (MPCA); in fact, the suggestion was offered that the significant relative risk for malignant lymphoma caused by exposure of phenoxy herbicides in general could be attributed to immunologic depression or mutagenic effects caused by 2,3,7,8-TCDD. Eriksson et al. (1981), on the other hand, attempted to calculate relative risk to development of soft-tissue tumors among men exposed to phenoxy herbicides that were uncontaminated (2,4-D; MPCA) with 2,3,7,8-TCDD but this population consisted of only 7 cases and 4 controls. The Swedish studies, despite serious problems of potential influence of contaminants, small populations in some instances, and recall bias, make a strong case for phenoxy herbicide-related occupational carcinogenesis. Causation by any specific herbicide, however, remains uncertain.

Cases of soft tissue sarcoma have also been reported in the United States among chemical industry workers exposed to varying levels of 2,4,5-T, 2,4,5-TP, chlorophenols, 2,3,7,8-TCDD and other industrial chemicals (Cook, 1981; Moses and Selikoff, 1981). Honcher and Halperin (1981) reported that 3 of 105 deaths reported by two chemical companies were due to soft tissue sarcoma. This represents a 2.9% mortality rate, while only 0.07% of deaths in United States males were due to soft tissue sarcoma. The few cases reported and contaminant chemical influence preclude any conclusion regarding the causative agent or agents.

A positive association between 2,4,5-T usage and increases in birth defects or abortions has been reported in human populations in Oregon (U.S. EPA, 1979b), New Zealand (Hanify et al., 1981) and Australia (Field and Kerr, 1979). A lack of any such association has been reported in human populations in Arkansas (Nelson et al., 1979), Hungary (Thomas, 1980), New Zealand (Department of Health, New Zealand, 1980; McQueen et al., 1977; Smith et al., 1982) and Australia (Aldred, 1978). As a result of difficulties in distinguishing the effects of 2,4,5-T from those of 2,3,7,8-TCDD contamination or other herbicides, none of the reportedly positive associations unequivocally identify 2,4,5-T as a causative agent. Similarly, the reportedly negative associations do not rule out 2,4,5-T as a potential teratogen or abortifacient in humans. Although these studies undoubtedly deserve a detailed review and assessment by experts in the fields of teratogenicity and epidemiology, such a review would exceed the resources available for the preparation of this document. Consequently, the following discussion will simply attempt to highlight the major findings and areas of uncertainty or controversy in each of the studies mentioned above.

Based on a report of strong evidence of abortions in a small group of women living around Alsea, Oregon, who may have been exposed to 2,4,5-T from aerial spraying (Smith, 1979), the U.S. EPA (1979b) initiated a study, often referred to as the "Alsea II study," to determine if spontaneous abortion rates evidenced seasonal variation in these two groups, and if such seasonal variations were associated with 2,4,5-T spray application. Upon completion of the study, the U.S. EPA made the following conclusions:

1. The 1972-1977 Spontaneous Abortion Rate Index (defined by U.S. EPA as "basically the ratio of the number of hospitalized spontaneous abortions to the number of births corresponding to the spontaneous abortions, based on the residence zip code of the women contributing to each event") for the study area was significantly higher than in the Rural Control Area or the Urban area.
2. There was a statistically significant seasonal cycle in the abortion index in each of the areas with a period of ~4 months. In particular, there was an outstanding peak in the study area in June.
3. There was a statistically significant cross-correlation between the Spontaneous Abortion Rate Index and spray patterns in the study when a lag-time of 2 or 3 months was included.

The U.S. EPA concluded, however, "This analysis is a correlational analysis, and correlation does not necessarily mean causation." Milby et al. (1980), citing three critiques of the Alsea II study that were not published in the open literature, state that the statistical method and basic design of the Alsea II study were sufficiently flawed to make this study of no use in human risk assessment. Based on a report by Smith (1979), the U.S. EPA has attempted to correlate 2,3,7,8-TCDD levels in the affected areas with the observed rate of abortion. No published reports have been encountered on the outcome of this effort.

In the only other report encountered on a population in the United States, Nelson et al. (1979) noted a general increase in the reported

incidence of facial cleft in both high and low exposure groups in Arkansas from 1948-1974. In this study, exposure estimates were based on average rice production in different areas of Arkansas, and the incidence of cleft palate was determined by screening birth certificates and checking records of the Crippled Children's Services. No consistent exposure/effect correlations were noted and the general increase with time in the incidence of facial clefts was attributed to better reporting procedures.

Because of the equivocal results of the Oregon study (U.S. EPA, 1979b), a feasibility study was conducted to consider research strategies and populations that could be used to generate evidence that can be more readily interpreted (Hatch and Kline, 1981). The researchers concluded that the Arkansas timber and rice areas are likely to permit a more thorough examination of the relation of 2,4,5-T exposure to spontaneous abortion than the Pacific Northwest timber areas. Arkansas appears to provide a unique setting for such a study in that the effects of chronic (i.e., forested areas), sporadic (rice-producing areas) and control (soybean-producing areas) exposure can be examined in comparable populations.

Of the four reports available from New Zealand (Department of Health, New Zealand, 1980; McQueen et al., 1977; Hanify et al., 1981; Smith et al., 1982), the report by the Department of Health is essentially anecdotal, involving two women who gave birth to malformed children (one with an atrial septal defect and a malformation of the tricuspid valve of the heart and the other with biliary atresia). In both

cases, exposure to 2,4,5-T could not be ruled out. Based on an analysis of spraying records, the time course of the pregnancies, and plant damage near the women's homes, however, the Department of Health, New Zealand (1980) concluded that there was insufficient evidence to implicate 2,4,5-T spraying as a causative factor. Even if the spraying had been implicated, a lack of information on 2,3,7,8-TCDD levels in the spray and the absence of any monitoring data on 2,4,5-T or 2,3,7,8-TCDD would limit the usefulness of this report.

Of the other three studies from New Zealand, one (McQueen et al., 1977) is not published in the open literature but is summarized by Milby et al. (1980). According to the summary, McQueen et al. (1977) "...examined the epidemiology of neural-tube defects in three areas in New Zealand and concluded 'there is no evidence to implicate 2,4,5-T as a causal factor in human birth defects.'" No additional details are provided in the Milby et al. (1980) summary. A more recent published report from New Zealand (Hanify et al., 1981) noted a statistically significant association between levels of 2,4,5-T spraying and the occurrence of talipes, congenital defects of the foot, but no association with several other defects including anencephaly, spina bifida, cleft lip, isolated cleft palate, all heart malformations, and hypospadias or epispadias. The incidence of birth defects was obtained from an examination of hospital records in seven mutually exclusive areas of Northland, New Zealand, for each month over the period extending from 1960-1977. Exposure estimates were based on public, and presumably complete, records of aerial spraying along with a model that factored in assumed fractional rates per month of teratogen removal of 0.15 or 1.0. The statistically significant association was obtained only in the analysis

using an assumed fractional removal rate of 0.25, which is more realistic than the 1.0 estimate. Subanalyses by race (Caucasians and native Maoris) indicated no race dependence on the association.

The most recent study of New Zealand 2,4,5-T sprayers compared the prevalence of congenital defects, miscarriages and stillbirths between 2,4,5-T-exposed sprayers, non-2,4,5-T-exposed sprayers and nonsprayers (Smith et al., 1982). Congenital defects occurred in 13 of 427 (3%) normal births in the 2,4,5-T-exposed group, while 4/100 (4%) and 9/352 (2.6%) were reported in the non-2,4,5-T-exposed sprayers and nonsprayers groups, respectively. No specific defect was more prevalent. Miscarriages occurred in 43/427, 9/100 and 40/352 of normal births among the respective groups. Three stillbirths were reported in the 2,4,5-T sprayer group, while none were reported in either unexposed group. The relative risks of congenital defects and miscarriages were 1.19 and 0.89, respectively, for the 2,4,5-T exposed group. (Low incidences prevented relative risk calculations for stillbirths.) This study, therefore, shows no apparent association between 2,4,5-T exposure and congenital defects and miscarriages (Smith et al., 1982).

The three reports from Australia (Aldred, 1978; Field, 1978; Field and Kerr, 1979) also present apparently conflicting results. The report by Aldred (1978) is not published in the open literature, but the following is taken from Milby et al. (1980): "The report concluded that birth defects in a group of babies born in the [Yarram] district in 1974 and 1976 could not be attributed to exposure to 2,4,5-T or 2,4-D." Additional details that might be useful in assessing the significance of this statement are not

provided in the Milby et al. (1980) summary. The reports by Field (1978) and Field and Kerr (1979) noted a "linear correlation" between the incidence of neural-tube defects (anencephaly and meningomyelocele) in New South Wales, Australia, over the years 1965-1975, and the previous year's usage of 2,4,5-T in all of Australia. The authors noted a departure from linearity (a decrease from the expected incidence of neural-tube defects) in 1975 and 1976, when Australia instituted monitoring of 2,4,5-T to ensure a 2,3,7,8-TCDD level <0.1 ppm. Although Field and Kerr (1979) indicate that they consider the epidemiology data on neural-tube defects to be "relatively complete," they do not comment on the increasing incidence of neural-tube defects with time and whether or not an increase in the thoroughness of reporting neural-tube defects could have contributed to the apparent correlation of 2,4,5-T exposure with these defects. A visual replotting of the data suggests that the incidence of cleft palate correlates better with 2,4,5-T usage than with time. Nonetheless, the appropriateness of correlating 2,4,5-T usage in all of Australia with the incidence of defects in one area of Australia is questionable.

Thomas (1980) used an approach similar to that of Field and Kerr (1979) on data from Hungary. One major difference, however, is that Thomas (1980) compared the incidence of stillbirths, cleft lip, cleft palate, spina bifida, anencephalus and cystic kidney disease in all of Hungary between 1976 and 1980 with 2,4,5-T use in the previous year in all of Hungary. Because Hungary requires compulsory notification of malformations diagnosed from birth to age 1 year, because a relatively large percentage (55%) of the Hungarian population lives in rural areas where 2,4,5-T exposure may be expected to be greatest, and because annual use of 2,4,5-T in Hungary had

risen from 46,000 kg in 1969 to 1,200,000 kg in 1975. Thomas (1980) considered Hungary to be "...probably the best country in which to examine possible health effects of this herbicide." In any event, all indices of birth defect rates decreased or remained stable over the period of study.

Contaminants

Early studies using 2,4,5-TP and 2,4,5-T must be interpreted cautiously because the herbicide samples may have been contaminated with fairly high concentrations of 2,3,7,8-TCDD.

Summary

Occupational exposure to 2,4,5-TP and 2,4,5-T (along with other chemicals such as 2,4-D, di- and triphenols and 2,3,7,8-TCDD) resulted in reduced nerve conduction velocities (Singer et al., 1982). Case-control epidemiological studies of populations in Scandinavian countries exposed to the phenoxy herbicides (as well as other chemicals and contaminants) indicate excess risk to the development of soft-tissue sarcomas and malignant lymphomas (Axelson and Sundell, 1974, 1977; Axelson et al., 1979; Hardell, 1977; Hardell and Sandstrom, 1979; Eriksson et al., 1981; Hardell et al., 1981; Riihimaki et al., 1978). Results of reanalysis of these data by the CAG indicate a causal relationship between phenoxy herbicide exposure and sarcoma risk (U.S. EPA, 1980).

In the United States, cases of soft tissue sarcoma in workers exposed to industrial and agricultural chemicals including 2,4,5-TP and 2,4,5-T have been reported (Cook, 1981; Moses and Selikoff, 1981; Honcher and Halperin, 1981). Causation by any specific herbicide, therefore, is uncertain.

A positive correlation between 2,4,5-T usage with increased rates of spontaneous abortion and birth defects have been reported for human populations in Oregon (U.S. EPA, 1979b), New Zealand (Hanify et al., 1981) and Australia (Field and Kerr, 1979). Again, such correlations (not causations) are confounded by co-exposure to other chemicals and contaminants. A lack of correlation of reproductive and teratogenic effects with phenoxy herbicide exposure was reported for human populations in Arkansas (Nelson et al., 1979), Hungary (Thomas, 1980), New Zealand (Department of Health, New Zealand, 1980; McQueen et al., 1977; Smith et al., 1982) and Australia (Aldred, 1978). The possible contamination of 2,4,5-TP and 2,4,5-T with 2,3,7,8-TCDD and other impurities must be taken into account when assessing the effects of phenoxy herbicides.

VII. MECHANISMS OF TOXICITY

Pertinent data regarding the mechanisms of toxicity of 2,4,5-TP could not be located in the available literature.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$ADI = \frac{(\text{NOAEL or LOAEL in mg/kg/day}) (\text{body weight in kg})}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$AADI = \frac{ADI}{\text{Drinking water volume in l/day}} = \text{mg/l}$$

where:

NOAEL = no-observed-adverse-effect level

LOAEL = lowest-observed-adverse-effect level

Body weight = 70 kg for adult or 10 kg for child

Drinking water volume = 2 l/day for adults or 1 l/day for children

Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited

period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1980) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identifying a LOAEL (but not NOEL/NOAEL) for one or more species are available.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (however, 2,4,5-TP is not a carcinogen), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans from these data, it must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 l of water/day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude. The multistage model does not necessarily give the highest or lowest risk estimates at low doses. Whether it is the most conservative, least conservative or predicts a risk in the middle of the range of risks predicted by other models is chemical-specific. The multistage model is used because CAG and NAS use it.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have

been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results, and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Existing Guidelines, Standards and Recommendations for 2,4,5-T and 2,4,5-TP

The National Interim Primary Drinking Water Regulations (U.S. EPA, 1979a) allows up to 10 ppb of 2,4,5-TP in drinking water.

The National Academy of Sciences (NAS, 1977) has suggested an ADI for humans of 0.00075 mg/kg/day for 2,4,5-TP based on a NOAEL of 0.75 mg/kg/day and a 1000-fold uncertainty factor. The NOAEL was estimated from a 2-year feeding study performed by Mullison (1966) on the dog. NAS (1977) has suggested a NOAEL for 2,4,5-TP in drinking water of 0.00525 mg/l, assuming that 20% of the total ADI comes from this source and 2 l of contaminated water are consumed/day.

Exposure to high levels of 2,4,5-TP would most likely occur during the manufacturing and formulating processes, during spray operations for weed control, or in forestry and rangeland operations. The other major group at

risk from reproductive and teratogenic effects are women of child-bearing age who are employed in such occupations as foresters, pesticide applicators, highway construction and maintenance equipment operators. Precautions should be exercised in such operations to the greatest possible extent.

Noncarcinogenic Effects

Contamination of 2,4,5-TP with 2,3,7,8-TCDD may have been responsible for some of the biological effects reported herein. Most of the data have been obtained from the summaries of the health effects data published by Dow Chemical Company and they did not report the extent of contamination of the product. However, it is known that for registration of the product with the U.S. EPA, 2,4,5-TP is required to have <0.1 ppm 2,3,7,8-TCDD as a contaminant.

The summary data indicate single dose oral LD₅₀s for 2,4,5-TP range from 600-1000 mg/kg bw for mice, rats, guinea pigs and rabbits for acid and ester formulations; for the acid, an LD₅₀ of 650 mg/kg was determined in rats (Rowe and Hymas, 1954). Gross general symptoms of intoxication include depression, posterior quarter muscle weakness, irritation of the stomach and minor liver and kidney damage.

2,4,5-TP appears to be more toxic than 2,4,5-T in rats when administered orally over a prolonged period. Oral administration of 5 mg/kg bw/day of 2,4,5-TP to rats for 90 days in the diet produced histopathologic changes in the liver and kidney (Dow Chemical Company, 1962), whereas a dose of 2 mg/kg bw/day was reported to be a NOEL in dogs (parameters measured were not reported in NRCC, 1978) (Dow Chemical Company, 1963).

The only information available on the chronic toxicity of 2,4,5-TP (other than oncogenic study) comes from unpublished investigations in rats and dogs conducted by Dow Chemical Company. A 2-year dietary regimen of a potassium salt of 2,4,5-TP (0, 0.26, 0.8, 2.6 or 7.9 mg a.e./kg bw/day) only revealed a significant increase in relative kidney:body weight ratios in male rats at all doses and decreased body weight in male rats at the highest dose (Gehring and Betso, 1978). Due to the absence of morphological alterations in the kidney at any dose level, these investigators felt that the increase in kidney weight reflected a physiological adaptation rather than an untoward effect (Gehring and Betso, 1978).

Evidence of adverse effects on the livers of male dogs, however, was observed at 2.6 mg a.e./kg bw/day 2,4,5-TP. Both male and female dogs were affected at doses of 8.2 and 9.9 mg a.e./kg bw/day, respectively (Gehring and Betso, 1978). This 2-year feeding study of 2,4,5-TP resulted in mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation in females, accompanied by elevations of SGOT and SGPT levels. A 0.9 mg a.e./kg bw/day was judged to be a NOAEL for the male dog and 2.6 mg/kg/day for female dogs.

In addition to limited information from classical toxicological studies (such as acute, short-term or chronic) little information is available concerning the teratogenic potential of 2,4,5-TP. Two studies have been encountered on the potential teratogenic activity of 2,4,5-TP. Courtney (1977) administered 2,4,5-TP to pregnant CD-1 mice at a dose level of 1.5 mM/kg/day (398 mg/kg/day) on days 12 through 15 of gestation. The compound was administered both by gavage using corn oil:acetone (9:1) as the vehicle

and by s.c. injection using DMSO as the vehicle. Both administrations caused a significant ($p < 0.01$) increase in maternal weight, probably due to increased liver weight, and a significant increase ($p < 0.01$) in maternal liver-to-body weight ratios. Both routes of exposure were also associated with a significant ($p < 0.01$) decrease in fetal weight. Oral and s.c. exposures to 2,4,5-TP were associated with respective 7 and 3% incidences of cleft palate in total fetuses.

The other study on the teratogenicity of 2,4,5-TP is an unpublished study by Dow Chemical Company, summarized in U.S. EPA (1979a). Because the summary is so brief, it is reproduced in full below:

Dow Chemical Company studied the reproductive effects of silvex and the propylene glycol butyl ether ester of silvex (silvex-PGBE), each containing < 0.5 ppm TCDD. Sprague-Dawley rats were exposed to 25-100 mg/kg of silvex on days 6-15 of gestation. Significant effects on fetal mortality and birth weight were observed in the litters of treated dams. Skeletal anomalies, such as cleft palate, retarded ossification and extra cervical ribs were observed among the exposed fetuses. Microphthalmia (abnormal smallness of the eyeball) and cardiovascular abnormalities were also seen. Similar effects were observed when animals were dosed with silvex-PGBE, or when dosed for three-day intervals during the period of early organogenesis.

Quantification of Noncarcinogenic Effects

1-Day Health Advisory. The available data are inadequate to derive a 1-day HA. No quantitative data on acute exposure of humans to 2,4,5-TP were available. All information on single oral exposure of laboratory animals is concerned with lethality. The oral LD_{50} s range from ~600-650 mg/kg in the rats; 750-819 mg/kg in rabbits; 1250 mg/kg in guinea pigs and 1410 mg/kg in mice for acid and ester formulations (Rowe and Hymas, 1954). General symptoms of acute toxicity include muscle weakness, irritation of the stomach and minor damage to the liver and kidney.

10-Day Health Advisory. There is concern that 2,4,5-TP might be a teratogen since there is evidence that a similar herbicide, 2,4,5-T, is a teratogen; however, little information is available on the teratogenic or reproductive effects of 2,4,5-TP or its esters, and the available data are inadequate for determining a 10-day HA using teratogenicity as an endpoint. Only two animal teratogenicity studies have been conducted. These two studies involved oral administration of 2,4,5-TP or the propylene glycol butyl ether ester of 2,4,5-TP during gestation: the first in CD-1 mice (Courtney, 1977) and the second in Sprague-Dawley rats (U.S. EPA, 1979a). The only dose tested in mice by the oral route, ~389 mg/kg/day on days 12 through 15 of gestation, produced cleft palate in 7% of the exposed fetuses as compared with 0% in the controls. In rats, the lowest dose tested, 25 mg/kg/day on days 6-15 of gestation, also resulted in a significant increase in cleft palate as well as retarded ossification, other skeletal anomalies and increased fetal death. Although it appears that 2,4,5-TP is somewhat less potent than 2,4,5-T, the complex pattern of dose and dose schedule on the apparent activity of these compounds (Courtney, 1977) precludes use of data on 2,4,5-T to derive a 10-day HA for 2,4,5-TP by analogy.

Two unpublished studies by Dow Chemical (1962, 1963) that described the toxicity of 2,4,5-TP to rats and dogs were located. No effects were reported in dogs administered 2 mg/kg/day 2,4,5-TP in the diet for 89 days. Only one dose level was employed in this study, and the available description of this unpublished work provided no detail on the extensiveness of pathologic examination. In a companion study, rats administered 5 mg/kg/day of the sodium salt or PGBE ester of 2,4,5-TP for 90 days had an increase in relative weight of the liver and kidney with "histopathologic changes" in both.

Of these two studies, the study using the dog that identified a NOEL of 2 mg/kg should preferentially be used to calculate a 10-day HA. The calculations for a 10 kg child consuming 1 l of water/day and for a 70 kg adult consuming 2 l of water/day are given below:

For a 10 kg child:

$$\frac{2 \text{ mg/kg/day} \times 10 \text{ kg}}{1 \text{ l/day} \times 100} = 0.20 \text{ mg/l}$$

where:

2 mg/kg/day = no observed effect level in dogs

10 kg = assumed average weight of a child

1 l/day = assumed consumption of drinking water by a child

100 = uncertainty factor

For a 70 kg adult:

$$\frac{2 \text{ mg/kg/day} \times 70 \text{ kg}}{100 \times 2 \text{ l/day}} = 0.70 \text{ mg/l}$$

where:

2 mg/kg/day = no observed effect level

70 kg = assumed average body weight of an adult

2 l/day = assumed consumption of drinking water by an adult

100 = uncertainty factor

Lifetime Adjusted ADI. Lifetime ADIs are normally derived from 2-year feeding studies in animals. The animal species which is most sensitive to the toxic effects or the species which metabolizes the compound in a manner similar to that in man is selected for estimating ADIs for humans. In these studies, a no adverse health effects level is identified. This level is divided by an uncertainty factor which may vary from 10-1000 based on the overall scientific judgment to determine an ADI.

In 1976, the U.S. EPA, Office of Drinking Water established an interim primary drinking water standard of 0.01 mg/l. This was based on a Dow Chemical Company study on dogs. In this study, a NOAEL of 0.9 mg/kg was divided by an uncertainty factor of 500 and a final standard of 0.01 mg/l was calculated for a 70 kg adult consuming 2 l of water/day. This standard is 20% of the total ADI.

The NAS (1977) recommended a concentration of 0.00525 mg/l 2,4,5-TP in drinking water, based on an ADI of 0.0525 mg/day (or 0.00075 mg/kg/day) and 2 l of water/day assuming that 20% of the total ADI comes from drinking water. This recommendation was based on a 2-year study reported by Mullison (1966) on dogs. The NAS calculated the ADI value from a NOAEL of 0.75 mg/kg/day and a 1000-fold uncertainty factor.

Limited chronic oral toxicity data are available for 2,4,5-TP to derive an ADI. For example, Gehring and Betso (1978) reviewed data from Dow Chemical Company unpublished studies in which the potassium salt of 2,4,5-TP (2,3,7,8-TCDD content not specified) was administered to Wistar rats and Beagle dogs for 2 years in the diet. The LOAEL in dogs, a more sensitive species than rats to phenoxy herbicides, was reported to be 2.6 mg a.e./kg bw/day, which produced mild hepatocyte necrosis in males (see Table V-8), while the next lower dose of 0.9 mg a.e./kg/day produced no pathologic effects (i.e., a NOAEL). In rats doses as low as 0.26 mg a.e./kg bw/day produced an increase in relative kidney weight (statistical significant not specified); but the investigators thought that in the absence of histological pathology that this effect reflected a physiological adaptation rather than an adverse effect. In early subchronic studies, however, Dow

Chemical Company (1962) reported that the dietary administration of the sodium salt or the PGBE ester of 2,4,5-TP resulted in "histopathologic changes" in the liver and kidneys of rats receiving 5 mg a.e./kg bw/day for 90 days.

Based on previous guidelines (U.S. EPA, 1980) it appears that the most appropriate dose level from which to estimate an ADI would be the male dog NOEL of 0.75 mg/kg bw/day (Mullison, 1966)*, since it represents the highest exposure level that produced no signs of toxicity in what appears to be a more sensitive species than the rat. The results of this study are confirmed by Gehring and Betso (1978).

A lifetime AADI of 0.26 mg/l for an adult can be calculated by multiplying the animal dose (0.75 mg/kg/day*) by the assumed body weight of an adult (70 kg) and dividing by an uncertainty factor of 100 and the assumed consumption of 2 l of water/day. This safety factor is appropriate for extrapolating from an animal NOEL; it is designed to protect the most sensitive members of the human population and to allow for possible differences in the sensitivity between species in extrapolating from an animal study to humans.

$$AADI = \frac{0.75 \text{ mg/kg/day} \times 70 \text{ kg}}{2 \text{ l/day} \times 100} = 0.26 \text{ mg/l}$$

*As calculated by the NAS and accepted by the Office of Pesticide Program of the U.S. EPA.

To equate this AADI with that of the NAS recommendation and with interim primary drinking water standards, the AADI should be divided by a factor of 5 which relates to 20% of the total ADI (i.e., $0.26 \div 5 = 0.052$ mg/l). It is clear that the criteria document value is ~10 times higher than the NAS recommendation and 5 times higher than the interim primary drinking water standards.

Summary

The 1-day, 10-day and lifetime HAs calculated for 2,4,5-TP are summarized in Table VIII-1. The data demonstrate that as the length of exposure increases, the recommended "safe" dose levels for a child or adult decreases. These dose levels derived from data on experimental animals are designed to protect the most sensitive members of a population from chronic and short-term exposure to 2,4,5-TP in drinking water.

Carcinogenic Effects

Limited data concerning the potential carcinogenicity of 2,4,5-TP are available. Chronic oral exposure to 2,4,5-TP did not elicit significantly increased incidences of tumors at any site in two strains of mice exposed to 17.2 mg/kg/day for 80-81 weeks (Bionetics Research Laboratories, 1968; Innes, 1969), in rats exposed to 7.9 mg a.e./kg/day for 2 years (Gehring and Betso, 1978) or in dogs exposed to 9.9 mg a.e./kg/day for 2 years (Gehring and Betso, 1978).

TABLE VIII-1

Summary of Calculated Health Advisories for 2,4,5-TP

Health Advisory	NOEL or LOAEL	Species	Effect	Calculated Level for Safe Exposure		Reference
				Child	Adult	
1-Day	No available data					
10-Day	2 mg/kg/day (NOEL)	rat	histopathological effects in kidney and liver at higher doses	0.20 mg/l (0.20 mg/day)	0.70 mg/l (1.4 mg/day)	Dow Chemical Co., 1963
Lifetime AADI	0.75 mg/kg/day* (NOAEL)	dog	mild hepatocyte necrosis in males at higher doses	NA	0.26 mg/l (0.52 mg/day)	Mullison, 1966

*As calculated by the NAS and accepted by the Office of Pesticides Programs of the U.S. EPA.

NA = Not applicable

Innes et al. (1969) reported that tumor incidences were not increased at any site in B6C3F1 or B6AKF1 mice (18/sex/strain) that were treated orally by gavage from 7-28 days of age with 46.4 mg/kg bw/day of 2,4,5-TP, and subsequently maintained for 76-77 weeks on a diet that contained 121 ppm 2,4,5-TP. If it is assumed that mice consume 13% of their weight in feed each day, the estimated daily TWA dose of 2,4,5-TP is 17.2 mg/kg/day. Elevated incidences of tumors were also not observed at specific sites in the same strains of mice (18/sex/strain) 18 months after single s.c. injections of 215 mg/kg 2,4,5-TP (in DMSO) on day 28 of age. Complete necropsies that included gross and histological examination of major organs and tissues were performed on all treated and control animals. Male B6C3F1 mice that were treated orally or by s.c. injection did show a higher incidence of total tumors (8/17 and 7/18 in treated vs. 22/79 and 2/24 in controls, respectively), but this was not apparent in female B6C3F1 or B6AKF1 mice of either sex.

Gehring and Betso (1978) reported that the Dow Chemical Company (unpublished studies) found no increased incidence of tumors in male or female Wistar rats that were fed 2,4,5-TP potassium salt at levels of 0, 0.26, 0.8, 2.6 or 7.9 mg a.e./kg bw/day for 2 years. Thirty animals of each sex were initially treated at each dose levels, and 3-5 rats/sex/dose were selected for interim sacrifices at 12 and 18 months.

Special Considerations

There is insufficient data on 2,4,5-TP to define high risk subpopulations, or the effects of simultaneous exposure to 2,4,5-TP and other pollutants.

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